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Abstract

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Project Title:	Small Molecule Inhibition of Staphylococcus Aureus Virulence

Abstract: *DESCRIPTION (provided by applicant):* Quorum sensing is a cell-to-cell communication system that permits members of a bacterial population to coordinate their behavior dependent on cell density. The mediators of this communication system are small, diffusible pheromones or autoinducers that are secreted by the bacteria and that accumulate extracellularly. At the appropriate concentration threshold that reflects a sufficient number or quorum of bacteria, the autoinducers signal gene expression programs that direct the coordinated action of the population. The list of bacterial pathogens that use this method of communication to regulate virulence is expanding and now includes some of the most common bacterial pathogens of humans including the medically important pathogen Staphylococcus aureus. Because antibiotic resistance is an emerging problem in this pathogen and vaccines are of limited efficacy, quorum sensing is becoming a therapeutic target for treatment of this infection. Attacking virulence by these strategies, termed "quorum quenching," has proven successful in two animal models of S. aureus infection. We recently published data demonstrating that phagocyte-derived reactive oxidants inactivate the peptide thiolactone autoinducer of S. aureus and that this is important for host defense against this infection (Rothfork et al, PNAS 101:13867, 2004). Our data demonstrate that targeting virulence by chemical inactivation of the quorum sensing pheromone represents a viable treatment option. We hypothesize that small molecule inhibitors of the peptide autoinducing pheromone (AIP) can abrogate virulence dependent gene expression. To test this hypothesis, we are applying to the Molecular Libraries Screening Centers Network (MLSCN) to pursue the following specific aims: Specific Aim #1: To screen libraries of small molecules in a high throughput fluorescence-based screening assay to identify compounds capable of suppressing pheromone-dependent activation of the promoter for a global regulator of Staphylococcus aureus virulence, RNAIII. Specific Aim #2: To confirm that the compounds that inhibit RNAIII promoter activation also inhibit expression of the virulence genes that are regulated by RNAIII.

Thesaurus Terms: Quorum sensing, Staphylococcus aureus, antibiotic resistance, quorum quenching, S. aureus infection, peptide thiolactone autoinducer of S. aureus,

peptide autoinducing pheromone, AIP, small molecule inhibitors, Molecular Libraries Screening Centers Network, MLSCN, high throughput screening, fluorescence-based screening assay, pheromone-dependent activation, RNAIII

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